## REMARKS

Claims 1, 6-8, and 14-17 are currently pending in the application. Claims 1, 6-8, and 14-17 are in independent form.

Claims 1, 6-8, and 14-17 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Office Action holds that Applicant has not described with sufficient clarity what statins and phosphodiesterase inhibitors are contemplated and the claims encompass any statin or phosphodiesterase (PDE) inhibitors known and unknown. No distinguishing features by members of those broad genera have been provided in the instant disclosure. The Office Action further holds that Applicant has only shown that PDE5 inhibitors induce cGMP in the previously submitted Declaration. In response thereto, Applicant submits herein a declaration stating that any phosphodiesterase inhibitor can be used and are contemplated by the presently pending claims. The previously submitted Declaration showed that any statin will work with the present invention. References cited below can be found in the declaration.

More specifically, the declaration states that other PDE inhibitors also work with the present invention because they elevate cGMP levels. Rat brain expresses PDE2, 5, and 9 genes (Van Staveren, et al. 2003). PDE2 regulates the basal cGMP concentration in thalamic neurons (Hepp, et al. 2007). A selective PDE2 inhibitor (Bay60-7550), a selective PDE5 inhibitor (sildenafil), and a selective PDE9 inhibitor (Sch51866) increase cGMP levels in cultured human retinal pigment epithelium (Diederen, et al. 2007) and regulate cGMP levels in rat spinal cord (de Vente, et al. 2006). Thus, all PDE inhibitors increase cGMP, not just PDE5, and the claims comply with the written description requirement. Reconsideration of the rejection is respectfully requested.

Claim 1 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Quast, et al. taken with Horackova, et al., in view of U.S. Patent No. 5,428,070 to Cooke, et al. Specifically, the Office Action holds that Quast, et al. teaches administering L-arginine (as N-monomethyl-L-arginine) to rats after ischemic stroke has occurred. Quast, et al. fails to teach identifying new neuron growth as required by the instant claim.

The Office Action holds that Horackova, et al. teaches more nitric oxide synthesizing neurons are present after the administration of a nitric oxide donor S-nitroso-N-acetylpenicillinamine implying new neurons are made, and the reference suggests SNAP augments neurons. Although Horackova, et al. did not use L-arginine, SNAP is a nitric oxide donor, and the Office Action holds that substituting one for the other is within the purview of one skilled in the art because both are nitric oxide donors and would be expected to function the same.

The Office Action further holds that Cooke, et al. discloses administering L-arginine after vascular injury with emphasis on decreasing the effects of atherogenesis, and atherosclerotic vascular diseases such as stroke are higher in patients with non-insulin-dependent diabetes mellitus wherein the conditions may result in stroke. The Office Action holds that the drug L-arginine is administered after the injury (post) and cGMP is increased resulting in new neuron growth.

Thus, the Office Action holds that one skilled in the art would have been motivated to administer L-arginine to patients post stroke in order to promote neurogenesis, or growth of new neurons, because L-arginine is the substrate for nitric oxide (NO) production and has been shown to induce an endothelium-dependent increase in cerebral blood flow in humans. The Office Action further holds that it would have been obvious to one skilled in

the art to combine the cited references and administer L-arginine in a post stroke event to a patient because the art teaches so and with regards to identifying increased numbers of new neurons, the teaching of Horackova, et al. indicates that more neurons are present since L-arginine increases the beating of myocytes. Reconsideration of the rejection under 35 U.S.C. §103(a) as being unpatentable over Quast, et al., Horackova, et al., and the Cooke, et al. patent is respectfully requested.

Quast, et al. has nothing to do with neurogenesis and recovery of function, especially by administering a NO donor. In fact, just the opposite is concluded from this reference: "In conclusion, we demonstrate for the first time that NO is an important mediator in hyperglycemic-exacerbated ischemic brain injury. By inhibiting NO production, low dose L-NAME dramatically attenuates injury to the brain cells and to the cerebral vasculature". In other words, Quast, et al. shows that the presence of NO is detrimental to ischemic brain damage. In contradistinction, the present invention demonstrates that NO donors and agents which increase NO and cGMP improve neurological function. From Quast et al, one would conclude the opposite and would not administer L-NAME to a patient.

Horackova, et al. investigates, in "culture", not *in vivo*, the interaction between cadiomyocytes and extracardiac and intrinsic cardiac neurons. The goal of this study is to determine the influence of these neurons on the beating frequency of the cardiac cells (myocytes). The conclusions of the study are 1) that NO sensitive neurons increase the beating rate of cardiomyocytes in the presence of NO; 2) more NO synthesizing neurons are present in intrinsic cardiac neurons versus extrinsic neurons; and 3) the beating rate of non-innervated myocyte cultures is not directly affected by NO.

Horackova, et al. has absolutely nothing to do with neurogenesis or recovery of brain function. Horackova, et al. simply demonstrates that certain

types of peripheral nerve cells can affect the beating of cardiac cells and that NO sensitive neurons alter the beating rate of heart cells. There is no logical or scientific connection between this study and the generation of new neurons, much less neurons within the subventricular zone of the brain. No neurons are generated in Horackova, et al.'s *in vitro* study using peripheral nerves. The data and conclusions are limited to the effect of NO sensitive neurons on the beating rate of cardiomyocytes.

In addition, the statement that, "Horackova... teaches more NO synthesizing neurons are present after the administration of a NO donor SNAP, implying new neurons are made" is an incorrect reading of the text. No neurons are made, only that there are more NO sensitive neurons within the heart than outside the heart, i.e. Stellate ganglion neurons. Also, the statement that "SNAP augments neurons" is incorrect. See the first paragraph of the Discussion in Horackova, et al., "SNAP ... enhanced the beating rate of myocytes... This indicates the presence of NO sensitive neurons in these co cultures". The statement by the Office Action that "quantities of neurons in different sites were compared", is also a misunderstanding of the Horackova, et al. text. Horackova, et al. note that more cardiac neurons are NO reactive than non-cardiac peripheral neurons; there is no change in the quantity of neurons, just that neurons within the cardiac muscle are somewhat different than neurons outside the cardiac muscle - they are NO sensitive and respond to agents like SNAP or L-Arginine. Thus, in contradistinction to the present invention, Horackova, et al. does not teach the production of new neurons.

The Cooke, et al. patent explicitly addresses the role of administering L-arginine as a substrate for nitric oxide (NO) in the treatment of atherosclerosis and restenosis. Although atherosclerosis is a minor risk factor for stroke, the reduction of atherosclerosis or restenosis of a coronary artery or even a cerebral artery (which is not the focus of the Cooke, et al.

patent) has nothing to do with neurogenesis, brain plasticity, and inducing recovery from stroke as in the presently pending application.

The basic chemistry of the NO pathway dictates that cGMP is increased in response to NO. Therefore, administering a NO substrate will, based on the laws of chemistry, increase cGMP. In example 2 of the Cooke, et al. patent, column 9, line 22, the text reads, "the reduction in platelet aggregation was associated with a two-fold increase in cGMP content in aggregated platelets from arginine treated animals". This is simple chemistry, that a substrate for NO will increase cGMP. There is, however, no statement or logical scientific connection that can be made relating cGMP to the induction of neurogenesis and recovery from stroke, as claimed by the presently pending independent claims. Nowhere in the Cooke, et al. patent, is there any statement or inference to the brain, to neurogenesis, to recovery from stroke and brain plasticity. Certainly Cooke, et al. does not disclose or suggest the presently added step to claim 1 of "identifying increased numbers of new neurons". One cannot infer in any way that a decrease in atherosclerosis and restenosis of a vessel is related to the production of new brain cells. The statements in the Cooke, et al. patent in column 3, lines 52-53 address the role of arginine and NO in restenosis, completely independent of neurogenesis, stroke, and recovery. This is a vascular issue about vessels that re-occlude and the rate of re-occlusion is reduced with these compounds. Likewise, the reference to col.9, lines 22-24, relates to the role of NO/L-arginine on aggregated platelets; again, not in anyway associated with the presently pending independent claims. The Cooke, et al. patent is directed towards a means to reduce vascular pathology, associated with atherosclerosis and re-occlusion of blood vessels. The presently pending claims are independent of vascular issues, and as discussed in the previously submitted Declaration, Applicants have also shown that agents which increase cGMP such as PDE5 inhibitors and statins act directly on neurons and progenitor cells in brain to induce the production of new neural cells.

None of the cited references teach the production of new neurons through the administration of the compounds of the present invention. Furthermore, Quast, et al. teaches away from the administration of NO donor compounds. Therefore, neither Quast, et al., Horackova, et al., or Cooke, et al. alone or in combination teach the required steps of the presently pending claims of producing new neurons and identifying new neurons.

Since neither the cited reference alone or in combination with knowledge in the art suggests the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

Claims 1, 6-8 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the Cooke, et al. patent taken with the Liao patent in view of the Kaposzta, et al. reference taken with the Ohtsuka, et al. reference, further in view of Quast, et al. taken with Horackova, et al. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the Cooke, et al. patent taken with the Liao, patent in view of the Kaposzta, et al. reference taken with the Ohtsuka, et al. reference, further in view of Quast, et al. taken with Horackova, et al. is respectfully requested.

As stated above, the Cooke, et al. patent does not disclose or suggest the present invention because there is no disclosure or suggestion of neurogenesis or increased neural function with the administration of the compounds along with identifying increased numbers of new neurons as required by the presently pending independent claims. Further combining Cooke, et al. with the above cited references does not arrive at the present invention.

The Office Action has held that the Liao patent teaches a surprising connection was made in connection with the treatment of ischemic stroke, wherein brain injury reduction is measured by determining a reduction in the infarct size in treated versus control groups. At column 8, lines 62-65 there is further disclosed that the "brain injury reduction, as demonstrated in the examples below, can be measured by determining a reduction in infarct size in the treated versus the control groups." In other words, the treatment is similar to that of the Moskowitz patent previously cited in the present application, which does not provide the same results as accomplished by the method of the presently pending claims.

Contrary to the statement that "L-arginine is known for its properties of promoting neurogenesis (see Moskowitz, of record)" made by the Office Action, Applicants have previously stated that Moskowitz discloses no such thing and in fact makes the statement that neurons cannot regenerate. Applicants note that no cited prior art reference to date has shown regeneration of neurons or new neuron growth. This was commonly accepted knowledge in the art at the time of the present invention, which is why the results of the present invention are so unexpected. Therefore, *none of the cited prior art can perform the required steps of claims 1 and 6-8 of "identifying increased numbers of new neurons"*. Further with respect to the statement made by the Office Action, Applicant has included new claims 14-17 which do not recite the compound "L-arginine". Moskowitz does not disclose any evidence that L-arginine can be effective after an ischemic event, and Moskowitz does not disclose the other compounds recited by the claims even capable of being used to treat after an ischemic event.

As was found with regard to the Moskowitz patent, the Liao patent merely discloses that stroke can be treated during a finite period of time. It is commonly known to those of skill in the art that there is a distinct period of time in which the damage occurring from a stroke can be mediated.

Subsequent to this time period, it was believed that treatment was futile. The Liao patent discloses at column 9, lines 21-30 that the treatment can either be prophylactic or can be acute. The acute treatment is defined as "at the onset of symptoms of the condition or at the onset of a substantial change in the symptoms of an existing condition." This definition is commensurate in scope with the knowledge of those of skill in the art defined above. Essentially, the Liao patent discloses treatment before or during the stroke itself in order to afford protection from stroke.

While Liao states that "the invention ... is useful for treating subjects with hypoxia-induced conditions", there is no reason to interpret this statement to mean that treatment is given after stroke as it must be read in the context of the whole patent disclosure (col. 3, lines 45-46). While conditions caused by hypoxia can be treated, this treatment is given prior to any hypoxia-induced event. There is no indication from the Liao patent that treatment can be given post ischemic event. Every example given by Liao is directed to prophylactic treatment before ischemia occurs, especially in Example 17 (simvastatin treatment for 14 days followed by production of cerebral ischemia). Furthermore, nowhere in the Liao patent is there any statement or inference to neurogenesis (i.e. the generation of new neurons), recovery from stroke with treatment after such stroke has happened, or recovery of brain plasticity as required by the presently pending independent claims.

Applicants previously presented a journal article by Liao (proc. Natl. Sci. USA, Vol. 95, pp. 8880-8885, July 1998) to further provide evidence that Liao only discloses prophylactic treatment or at most treatment during a stroke. This article also examines the effect of HMG-CoA reductase inhibiting drugs on ischemia through their mechanism of up-regulating endothelial nitric oxide synthase. The goal of the article is "to determine whether statin administration confers protection against ischemic stroke" and therefore

simvastatin was administered daily for 14 days to mice before MCA occlusion (p. 8881). Further, the authors state that "the major finding in this study is that prophylactic treatment with HMG-CoA reductase inhibitors protects against ischemic strokes after focal brain ischemia" (p. 8884). This article teaches much of the same methods and findings with simvastatin as the Liao patent. Accordingly, there is no motivation for treatment after the stroke is complete, i.e. post ischemic event, since this is a point in time substantially after the onset of the symptoms.

With regard to the Kaposta, et al. and Ohtsuka, et al. references, these references merely disclose use of compounds prophylactically. There is no disclosure for the use of the compounds post ischemic event for creating neurogenesis.

With regard to Quast, et al. and Horackova, et al., as stated above, Quast, et al. teaches away from using NO donors in the first place. Horackova, et al. has nothing to do with neurogenesis and merely teaches that cardiomyocytes are sensitive to NO and beat faster in the presence of NO, and that there are more NO sensitive neurons in cardiac tissue than outside.

Applicants note that none of the cited references disclose any evidence of the production of new neurons and the identification of new neurons.

Since none of the cited references alone or in combination with one another suggest the currently claimed invention, it is respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

Claims 14-17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,423,751 to Liao. Specifically, the Office Action holds that Liao teaches up-regulation of endothelial cell nitric oxide synthase expression by administration of HMG-Co reductase inhibitors for the treatment of stroke. Liao teaches a surprising connection was made in the treatment of ischemic stroke wherein brain injury reduction is measured by determining a reduction in the infarct size in the treated versus the control groups. The Office Action holds that Liao fails to teach neuron growth and identifying increased numbers of new neurons. However, based on the teaching from the background section indicating that in mammals nitric oxide is expressed in neurons of nitric oxide synthase and are expressed in endothelial cells of nitric oxide synthase. Thus, the Office Action holds that one skilled in the art would know that nitric oxide is responsible for neurogenesis.

As stated above, Liao does not disclose the required steps of the present invention, either alone or in combination with other cited references. No other references besides Applicants' own work has demonstrated that neurogenesis (i.e. production of new neurons) is even possible with the administration of NO donor compounds of the present invention. One skilled in the art would not have identified that NO donor compounds can be used to produce new neurons because this result has simply never been shown before Applicants' showing. The Office Action is using an incredible amount of hindsight to make its conclusions, but if this property was inherent to NO donor compounds, Applicants' result would have been found in some other reference.

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

"It is essential that 'the decisionmaker forget what he or she has been taught at trial about the claimed invention and cast the mind back to the time the invention was made ... to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art.'" *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (citing *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983)).

Therefore, since Liao alone or in combination with knowledge of one skilled in the art does not disclose the required elements of the pending claims of the present invention, the present invention is patentable over Liao and reconsideration of the rejection is respectfully requested.

Claims 1, 6-8, and 14-17 of this application have further been rejected as unpatentable based on provisional non-statutory obviousness-type double patenting over co-pending Application No. 10/500,694. These rejections can be readily overcome by the filing of a terminal disclaimer in compliance with 37 C.F.R. 1.321(c) or (d). Applicants stand ready to provide the appropriate terminal disclaimer upon the indication of the allowance of the pending claims.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, and the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In conclusion, it is respectfully submitted that the presently pending claims are in condition for allowance, which allowance is respectfully requested. Applicant respectfully requests to be contacted by telephone if any remaining issues exist.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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CERTIFICATE OF ELECTRONIC FILING VIA EFS-WEB

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I hereby certify that this correspondence is being electronically filed with the United States Patent & trademark Office on the above date.

Terry Horst